## REMARKS

On page 2 of the Office Action, the Examiner rejects Claims 20-21, 26, 29-30 and 41-42 under 35 U.S.C. § 102(b) as being anticipated by Davis et al (of record).

Further, the Examiner rejects Claims 20-21, 26 and 40-41 under 35 U.S.C. § 102(b) as being anticipated by Barth et al (of record).

In addition, on page 4 of the Office Action, the Examiner rejects Claims 20-21, 26, 29, 30 and 41-42 under 35 U.S.C. § 103 as being unpatentable over Davis et al.

Also, the Examiner rejects Claims 20-21, 26 and 40-41 under 35 U.S.C. § 103 as being unpatentable over Barth et al.

Specifically, the Examiner states that Applicants' claimed compounds are for treating diseases, such as inflammatory skin disorders, hypertrophic heart and heart failure. Further, the Examiner states that Davis et al teaches compounds which are useful for the treatment of inflammatory cardiovascular disorders and Barth et al teaches compounds which are useful in treating diseases of the heart, blood vessels, inflammatory processes and allergies.

The Examiner contends that Davis et al teaches species within the scope of the examples of the present claims, and methods of their use (see the Abstract and in Column 11, lines 28-37 thereof). Also, the Examiner states that Barth et al teaches specific examples of the instant compounds and methods of their use (see Column 11, lines 14-19 thereof).

For the following reasons, Applicants respectfully traverse the Examiner's rejections.

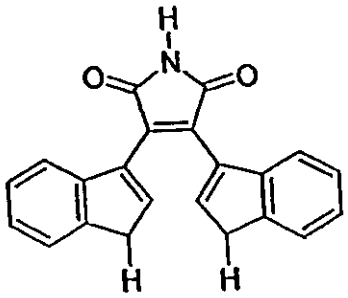
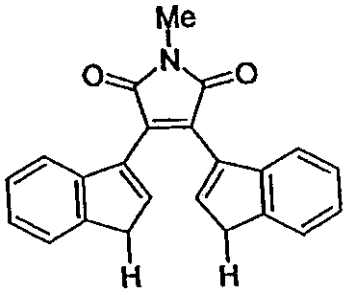
Applicants respectfully submit that Davis et al does not teach compounds within the scope of general Formula (I) of Claim 20 (as amended).

Applicants also respectfully submit that the Examiner's position on Claim 40 is incorrect *vis-à-vis* Barth et al. The specific examples of Barth et al pointed out by the Examiner have NH at the position of X in formula (I) of the present invention (i.e., X = $NR^5$, $R^5$ = a hydrogen atom). However, $R^5$ in Claim 40 does not represent a hydrogen atom. Thus, the subject matter of Claim 40 is not disclosed in Barth et al. Amended Claim 20 now recites the subject matter of Claim 40 (Claim 40 is now hereby cancelled), and thus Claim 20 is also novel over Barth et al.

As discussed above, in the compound of the present invention, X in formula (I) does not represent NH, whereas in the compound of Davis et al and Barth et al, the substituent corresponding to X in formula (I) represent NH. The differences between these compounds are discussed in the Amendment filed August 13, 2002, with respect to Toullec et al (*J. Biol. Chem.*, 266:15771 (1991)). As discussed in said Amendment, compounds having a substituent other than NH as X in formula (I) of the present invention have an unexpected superior effect in comparison with compounds having a substituent NH as X of

Davis et al and Barth et al. Inhibition of PKC is shown in Table I on page 15772.

INHIBITION OF PROTEIN KINASE C BY BISINDOLYL COMPOUNDS

| no. | structure | $IC_{50}$ (μM) |
|---|---|---|
| 3 |  | 0.01 ± 0.05 |
| 4 |  | > 50 |

The above Compound Nos. 3 and 4 correspond to Compounds 13 and 14, respectively, in Table 3 at page 37 of the present application. As shown above, Compound 13 is a potent PKC inhibitor, whereas Compound 14 does not significantly inhibit PKC. Accordingly, since PKC inhibiting activity does not predictably correspond to cell death inhibiting activity, the compounds of the present invention, which all having the cell death inhibiting activity, cannot be predicted from the cited references.

In particular, Barth et al teach the use of bisindolylmaleimide for the treatment of vascular diseases, such

as thrombosis, arterial sclerosis, and hypertension, etc., for the treatment of inflammatory processes, allergy, cancer and certain degenerative injury in the central nervous system, and for the treatment of diseases of the immune system and virus diseases. However, only one example is given as real test examples, showing inhibitory activities against some protein kinases and it is short of reasonable evidence demonstrating effectiveness in treating the enumerated diseases. Barth et al present no evidence for the causal and effect relationship between the above diseases and the activities inhibitory against PKC. Moreover, the present invention is concerned with drugs that inhibit cell death and their uses and is totally far from the concept of preexisting PKC inhibitors represented by Barth et al.

As to Davis, this reference teaches the use of bisindolylmaleimide for the treatment of acquired immune deficiency via the inhibition of HIV transfection and for the treatment of cardio-vascular diseases via their inhibitory effects on the contraction of smooth muscle cells. In fact, however, the test examples only show inhibitory activity for PKC, and thus it is short of reasonable evidence for the effectiveness on these disorders. Furthermore, the present invention does not describe the inhibition of HIV infection, but describes the inhibitory effect on cell death, and thus possesses conceptually different actions and different situations of use. In addition, regarding cardio-vascular diseases, the present invention is concerned with therapeutic drugs that involve the inhibition of cell death in cardiac cells which may occur during ischemia or under other various conditions. These therapeutic drugs are conceptually

different from pre-existing drugs which merely improve vascular circulation through vascular dilatation. The effect would not be easily expected by one of ordinary skill in the art.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Davis et al or Barth et al, and thus request withdrawal of the Examiner's rejections.

On page 6 of the Office Action, the Examiner rejects Claim 36 under 35 U.S.C. § 112, first paragraph.

Specifically, the Examiner contends that the specification is not enabled for "preventing functional deficiency of transplanted organs, tissues of cells". The Examiner recommends deleting the expression "preventing" from Claim 36 in order to overcome this rejection.

Applicants hereby amend the claims as suggested by the Examiner, thereby rendering moot the Examiner's rejection.

On page 7 of the Office Action, the Examiner rejects Claim 20 under 35 U.S.C. § 112, second paragraph.

Specifically, the Examiner states that the expression "inhibitor of apoptosis" is indefinite.

The Examiner's rejection can be overcome by amending Claim 20 to recite "a compound which inhibits apoptosis or necrosis".

Further, the Examiner rejects Claims 21-36 under 35 U.S.C. 112, second paragraph.

In view of the amendment to Claim 20, as discussed above, Applicants respectfully submit that the Examiner's rejection has been met.

In the paragraph bridging pages 7-8 of the Office Action, the Examiner objects to Claim 42, which refers to a "subject".

The Examiner's rejection has been met by amending Claim 42 to place such dependent upon Claim 41.

Finally, the Examiner objects to Claim 39 as being dependent upon a rejected claim, but indicates that such would be allowable if rewritten in independent form.

Applicants hereby amend Claim 39 to place such in independent form, as suggested by the Examiner.

In view of the amendments to the claims, and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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Date: February 24, 2003

## A P P E N D I X

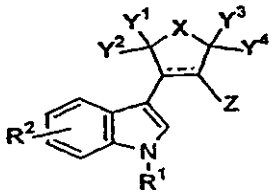
## Marked-Up Version of to Show Changes

IN THE CLAIMS:

Claim 40 is being cancelled.

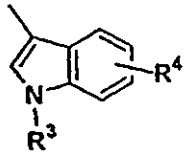
The claims are being amended as follows:

Claim 20. (Twice Amended) [An inhibitor of] A compound which inhibits apoptosis or necrosis represented by formula (I):



(I)

wherein X represents an oxygen atom or N-$R^5$; Z represents a halogen atom or



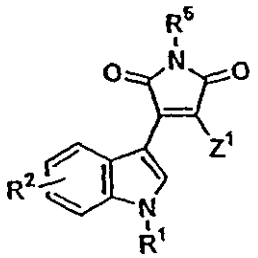
$R^1$ and $R^3$ each independently represents a hydrogen atom, an alkyl group which is substituted or unsubstituted, an alkenyl group which is substituted or unsubstituted, an alkynyl group which is substituted or unsubstituted, an aryl group which is substituted or unsubstituted, an acyl group which is substituted or unsubstituted, an alkoxy- or aryloxycarbonyl group which is substituted or unsubstituted, an alkyl- or arylthiocarbonyl group which is substituted or unsubstituted, an aminocarbonyl group which is substituted or unsubstituted, an alkyl- or arylsulfonyl group which is substituted or unsubstituted, an

alkoxyl group or an aryloxy group which is substituted or unsubstituted, or a hydroxyl group; $R^2$ and $R^4$ each represents substituent(s) on an indole ring, in which number and position (2-, 4-, 5-, 6-, or 7-position as position number of the indole ring) of the substituent(s) and kinds of the substituent(s) may be the same or different, and represents a hydrogen atom, an alkyl group which is substituted or unsubstituted, an alkenyl group which is substituted or unsubstituted, an alkynyl group which is substituted or unsubstituted, an aryl group which is substituted or unsubstituted, an acyl group which is substituted or unsubstituted, an alkoxy- or aryloxycarbonyl group which is substituted or unsubstituted, an alkyl- or arylthiocarbonyl group which is substituted or unsubstituted, an aminocarbonyl group which is substituted or unsubstituted, an alkyl- or arylsulfonyl group which is substituted or unsubstituted, an alkoxyl group or an aryloxy group which is substituted or unsubstituted, an alkyl- or arylthio group which is substituted or unsubstituted, a hydroxyl group, a carboxyl group, a cyano group, a nitro group, an amino group which is substituted or unsubstituted, or a halogen atom; $R^5$ represents an alkyl group which is substituted or unsubstituted, an alkenyl group which is substituted or unsubstituted, an alkynyl group which is substituted or unsubstituted, an aryl group which is substituted or unsubstituted, an alkoxyl group or an aryloxy group which is substituted or unsubstituted, an amino group which is substituted or unsubstituted, or a hydroxyl group[, or a hydrogen atom]; $Y^1$ and $Y^2$, and $Y^3$ and $Y^4$ each independently represent two hydrogen atoms or a hydrogen atom and a hydroxyl group, or are combined to form a carbonyl group; and $R^1$ and $R^2$, $R^1$ and $R^3$, $R^3$ and $R^4$, or $R^2$ and $R^4$ may be combined to form a

hydrocarbon chain or a hydrocarbon chain containing hetero atom(s) which is substituted or unsubstituted; and in the formula, the bond accompanying a dotted line represents a double bond or a single bond, or a pharmaceutically acceptable salt thereof.

Claim 36. (Amended) The composition of Claim 21, wherein said composition is useful for treating [or preventing] functional deficiency of transplanted organs, tissues or cells.

Claim 39. (Amended) A composition comprising, as an active ingredient, a 2-halo-3-indolylmaleimide compound according to formula (II):



(II)

where $Z^1$ represents a halogen atom; [and] $R^1$[, $R^2$ and $R^5$ have the same meaning as in Claim 20] represents a hydrogen atom, an alkyl group which is substituted or unsubstituted, an alkenyl group which is substituted or unsubstituted, an alkynyl group which is substituted or unsubstituted, an aryl group which is substituted or unsubstituted, acyl group which is substituted or unsubstituted, an alkoxy- or aryloxycarbonyl group which is substituted or unsubstituted, an alkyl- or arylthiocarbonyl group which is substituted or unsubstituted, an aminocarbonyl group which is substituted or unsubstituted, an alkyl- or arylsulfonyl group which is substituted or unsubstituted, an alkoxyl group or an aryloxy group which is substituted or

unsubstituted, or a hydroxyl group; $R^2$ represents substituent(s) on an indole ring, in which number and position (2-, 4-, 5-, 6-, or 7-position as position number of the indole ring) of the substituent(s) and kinds of the substituent(s) may be the same or different, and represents a hydrogen atom, an alkyl group which is substituted or unsubstituted, an alkenyl group which is substituted or unsubstituted, an alkynyl group which is substituted or unsubstituted, an aryl group which is substituted or unsubstituted, an acyl group which is substituted or unsubstituted, an alkoxy- or aryloxycarbonyl group which is substituted or unsubstituted, alkyl- or arylthiocarbonyl group which is substituted or unsubstituted, an aminocarbonyl group which is substituted or unsubstituted, an alkyl- or arylsulfonyl group which is substituted or unsubstituted, an alkoxyl group or an aryloxy group which is substituted or unsubstituted, an alkyl- or arylthio group which is substituted or unsubstituted, a hydroxyl group, a carboxyl group, a cyano group, a nitro group, an amino group which is substituted or unsubstituted, or a halogen atom; $R^5$ represents an alkyl group which is substituted or unsubstituted, an alkenyl group which is substituted or unsubstituted, an alkynyl group which is substituted or unsubstituted, an aryl group which is substituted or unsubstituted, an alkoxyl group or an aryloxy group which is substituted or unsubstituted, an amino group which is substituted or unsubstituted, a hydroxyl group, or a hydrogen atom; and $R^1$ and $R^2$ may be combined to form a hydrocarbon chain or a hydrocarbon chain containing hetero atom(s) which is substituted or unsubstituted, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Claim 42. (Amended) The method of Claim [40] 41, wherein said subject has a disease selected from the group consisting of neurodegenerative disease, neonatal jaundice, myasthenia gravis, brain ischemia, delayed neuronal death, ischemic heart disease, viral myocarditis, autoimmune myocarditis, a myocardial disorder, hypertrophic heart, heart failure, arrythmogenic right ventricular cardiomyopathy, alcoholic hepatitis, viral hepatitis, a renal disease, acquired immunodeficiency syndrome (AIDS), an inflammatory skin disorder, alopecia, graft versus host disease, a radiation disorder, a disorder due to a toxic agent, sepsis, osteomyelo-dysplasia, insulin dependent diabetes, and [aprion] a prion disease.